problems with drug-eluting coronary stents — the fda perspective

reports about resistance of the balloon to withdrawal attempts after the stent is deployed — a problem sometimes described as “stickiness” of the balloon during withdrawal. this problem does not appear to be related to the mechanical defect observed in the investigation of the balloon-deflation failures; rather, it seems to result from a combination of patient-related and device-related factors. these factors are still under review but are currently presumed to include friction between the stent-delivery balloon and the drug-polymer coating on the stent, as well as certain characteristics of the coronary vessel. the association, if there is any, between these reports of resistance to withdrawal and adverse clinical events is currently being assessed.

the boston scientific case illustrates the dilemma we face in determining the appropriate threshold for product recall and notification when the risk is of a severe but rare adverse event. in these cases, the potential benefit to be accrued from recalling the product must be balanced against the possible negative effects this action might have on public health. denying a potentially beneficial therapy to all patients, as in a complete recall of a product, might have greater adverse consequences than allowing the device to remain in use.

these cases exemplify the challenges that we face in regulating breakthrough technologies. in almost all instances, as in the cypher case, we do not have a complete accounting of all cases or information on the number of devices actually in use, making it impossible to compare similar products in terms of the rate of adverse events. our responsibility to protect the public health, however, necessitates that we consider early notification about any legitimate risk, weighing the risk posed by neglecting to notify practitioners about a clinically significant problem against the consequences of “crying wolf” on the basis of inconclusive information. in attempting to strike the right balance, we may engage clinical and other stakeholders for review and comment on our draft notifications before we release them. such a dialogue is particularly important in the case of breakthrough technologies, in which our decisions can have an immediate and profound effect on people’s lives.

from the center for devices and radiological health, food and drug administration, rockville, md.


on september 14, 2004, a food and drug administration (fda) joint advisory committee voted 15 to 8 to recommend that a “black-box” warning label be required for antidepressant drugs, indicating that they increase the risk of suicidal thinking and behavior (“suicidality”) in pediatric patients. although, as an epidemiologist and general pediatrician, i do not have clinical experience caring for depressed patients, after reviewing the evidence, i strongly favored the black-box warning.

treating depression in children

the editors asked two members of the psychopharmacologic drugs and pediatric advisory committees of the food and drug administration to comment on the committees’ recent recommendations regarding the use of antidepressant medications in children and adolescents.

their responses follow.

a black-box warning for antidepressants in children?

thomas b. newman, m.d., m.p.h.

on september 14, 2004, a food and drug administration (fda) joint advisory committee voted 15 to 8 to recommend that a “black-box” warning label be required for antidepressant drugs, indicating that they increase the risk of suicidal thinking and behavior (“suicidality”) in pediatric patients. although, as an epidemiologist and general pediatrician, i do not have clinical experience caring for depressed patients, after reviewing the evidence, i strongly favored the black-box warning.
During consideration of the proposed labeling change, the committee heard a number of presentations summarizing evidence that suicidality in children and adolescents may be increased by the newer antidepressant drugs, primarily selective serotonin-reuptake inhibitors. The most convincing evidence came from an FDA analysis of randomized trials. Most of these trials had been conducted by the drug manufacturers under the Best Pharmaceuticals for Children Act, which provides companies an additional six months of patent protection for their product if they do pediatric studies. These studies need not be published and need not be of high quality. In fact, we heard that because these medications are already widely prescribed "off-label" and patents may be close to expiration, sponsors may have more incentive to do the studies quickly than to do them well. To facilitate analysis of the patchwork of pediatric studies, the FDA obtained narratives of adverse-event reports from the trials and contracted with experts on suicide at Columbia University to review them. The Columbia staff members, who were unaware of the treatment-group assignments, were asked to determine whether the adverse events represented suicidality. FDA staff members then combined the results into a meta-analysis.

The results were striking. When all the pediatric trials were pooled, the rate of definite or possible suicidality among children assigned to receive antidepressants was twice that in the placebo group. (The summary risk ratio was 2.19; 95 percent confidence interval, 1.50 to 3.19.) Although the FDA staff did not provide this information to the committee, according to my own calculations, such a dramatic result would be expected to occur by chance only 1 time in 20,000 (P=0.00005).

Nonetheless, some FDA staff and committee members expressed reservations about the data used for this analysis. For example, there was a relatively small number of events, the trials had not been designed to evaluate suicidality, and the methods of ascertainment and classification of the events in the various trials were not uniform. To me, however, these concerns only made the results more compelling. Inadequate sample size and misclassification of outcomes make it more — not less — difficult to detect differences between groups in randomized, blinded trials. The fact that an association emerged from the meta-analysis with a P value of 0.00005, for an outcome that the sponsors of the trials were not looking for, and presumably did not wish to find, was quite convincing.

Inferences from the randomized trials were supported by public testimony from people who believed that antidepressant drugs had caused their loved ones to commit suicide (or, in some cases, homicide). Several of these cases involved patients who had shown no hint of suicidality before beginning treatment with the drugs and who had been given these drugs for indications other than depression, including migraine headaches, nail biting, anxiety, and insomnia.

Several committee members spoke in favor of the antidepressants, citing either their own clinical experience or the Treatment for Adolescents with Depression Study (TADS), a recently published randomized, double-blind study of fluoxetine for major depression in adolescents, which the committee reviewed in detail. However, others and I found the evidence of efficacy much less convincing than the evidence of harm. In reviewing TADS, we were struck by the small size of the difference between fluoxetine and placebo as compared with the effect of placebo alone. For example, after 12 weeks, the average decrease in the Childhood Depression Scale—Revised (scores on which were around 60 of a possible 113 at baseline in both groups, with higher scores indicating more severe depression) was 19.4 points with placebo, as compared with 22.6 points with fluoxetine (see Figure).
A Black-Box Warning for Antidepressants in Children?

It is easy to see why the personal experience of clinicians and patients would lead them to believe the drug to be effective, since they would have no way of knowing that more than 85 percent of the benefit they observed would also have occurred with placebo.

Randomized trials other than TADS have had less favorable results. The FDA indicated that only 3 of 15 trials of antidepressant use in children with depression had found a statistically significant benefit. The agency also provided us with a meta-analysis that showed that the estimated efficacy of antidepressants in children was minimal and likely to have been overestimated, because published studies have much more favorable results than unpublished studies. Thus, both clinical experience and published trials are likely to lead to inflated estimates of the efficacy of these drugs.

The committee members agreed that there are wide gaps in our knowledge about antidepressants. Perhaps the most important relate to their medium-term and long-term safety and efficacy. The FDA’s meta-analysis suggested that the new antidepressants double the risk of suicidality, from...
Antidepressants and Pediatric Depression — The Risk of Doing Nothing
David A. Brent, M.D.

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Eventually, we learned that depression did indeed affect children and adolescents. Through retrospective interviews with family members and friends, this disorder emerged as the single most important risk factor for adolescent suicide,


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